PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 16799/WO/03	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IL 03/00878	International filing date *(day/month/year)* 24.10.2003	Priority date *(day/month/year)* 25.10.2002
International Patent Classification (IPC) or national classification and IPC C07J21/00		
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.05.2004	20.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Deutsch, W Telephone No. +49 89 2399-8281

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-6, 8-100	as originally filed
7	filed with telefax on 02.12.2004

Claims, Numbers

1-22, 23 (part), 26 (part), 27, 28, 29 (part), 33 (part), 34-50	as originally filed
23 (part), 24, 25, 26 (part), 29 (part), 30-32, 33 (part)	filed with telefax on 02.12.2004

Drawings, Sheets

1/7-7/7	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-9,24-30,49,50

because:

☒ the said international application, or the said claims Nos. 26-30 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-9,24-30,49,50 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10-23,31-48
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	10-23,31-48
Industrial applicability (IA)	Yes:	Claims	10-23, 31-48
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Industrial Applicability

For the assessment of the present claims 26-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 26-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Clarity

Claims 1-9, 24-30, 49 and 50 are considered to be unclear, since they define the compounds in terms of functional definitions.

In claim 1 these functional definitions are a) "SOD mimic" component b) "NO donor" component.

The functional definitions used to define the solution is to the technical problem is the problem itself. In this case, it is considered that the invention can be defined otherwise without unduly limiting the claims, (e.g. by including the fulling structure), since the present claim would include compounds, which have not yet been invented.

It would be unclear to the skilled person what the actual structure of these components would be. Thus components ii) and iii) have potentially limitless structural potential placing an undue burden to find which variations fulfil the desired criteria, even where tests are available.

Furthermore the skilled person would not know which particular atoms in the molecule

should be considered, when testing for their ability to act as a SOD mimic or NO donor. The particular atoms could be part of the steroid component or acting as part of components ii) or iii) or of a substituent. Thus, the skilled person faced with a particular structure would not know with certainty, whether a compound fell under the said claims or not.

More specific definitions of SOD mimic groups and NO donors given in the description do not limit the claims.

V

Reference is made to the following documents

D1: US-A-5 750 744 (KING CHI-HSIN RICHARD ET AL) 12 May 1998 (1998-05-12)

D2: ZE'EV ZARETSKII AND L. KELNER: "Mass Spectrometry of Steroid Systems-XXII" TETRAHEDRON, vol. 31, 1975, pages 85-87, XP002275441

D3: KEANA, JOHN F. W. ET AL: "Synthesis of a novel cholesterol nitric oxide spin label. Application to the molecular organisation of human high density lipoprotein" J. AMER. CHEM.SOC, vol. 103, no. 16, 1981, pages 4904-4912, XP002275442

D4: DJERBASSI ET AL.: "Reaction of Steroidal Sapogenin Spiroketal with Ethanediol" J. ORG. CHEM., vol. 24, no. 1, 3 February 1959 (1959-02-03), pages 1-6, XP002275443

D5: SONDHEIMER F. ET AL.: "Steroids. LXVII. The Decarboxylation of Unsaturated Steroidal Acids. Synthesis of 17-Epitestosterone and 17-methylepitestosterone" J. AMER. CHEM. SOC, vol. 77, 1955, pages 4145-4149, XP002275444

D6: JONES, J. BRYAN AND GORDON, KEITH D.: "Micellar Aggregation and delat5-3-Keto Steroids Lacking a Polar C-17 Group and Its Relation to the Activity and Specificity of the delta5 to delta4-3-Ketosteroid Isomerase of Pseudomonas testosteroni" BIOCHEMISTRY, VOL. 12, NO. 1, 1973, vol. 12, no. 1, 1973, pages 71-76, XP002275445

D7: TSUJI, NATSUKO ET AL.: "Highly Stereoselective Hydrogenation of 3-oxo-4-ene and 1,4-diene Steroids to 5-beta Compounds with Palladium Catalyst" J. ORG. CHEM, vol. 45, 1980, pages 2729-2731, XP002275446

D8: HIRSCH A.F. ET AL: "Contagestational Agents. 1. Steroidal O-Aryloximes"

J. MEDICINAL CHEMISTRY, vol. 20, no. 12, 1977, pages 1546-1551, XP002275447

D9: WO 00/49993 A (WORCEL MANUEL ;GARVEY DAVID S (US); NITROMED INC (US)) 31 August 2000 (2000-08-31)

D10: US-A-5 707 984 (TJOENG FOE S ET AL) 13 January 1998 (1998-01-13)

D11 US-A-5 985 862 (CURRIE MARK G ET AL) 16 November 1999 (1999-11-16)

D12: US-A-3 054 812 (DANIEL BERTIN) 18 September 1962 (1962-09-18)

D13: US-A-3 215 713 (BARTON DEREK H R) 2 November 1965 (1965-11-02)

D14: US-A-3 014 932 (GEORGE ROSENKRANZ ET AL) 26 December 1961 n (1961-12-26)

Novelty

Claim 31 differs from compounds D1 to D8 and D10 through the introduction of a proviso that the compound contains at least one N-oxide free radical and at least one NO donor, wherin theNO donor group.

Inventive Step

D10 is considered to represent the closest prior art , since this discloses compounds useful in the treatment of inflammatory and auto immune illnneses as well as other disorders such asthma. Furthermore the compounds of D10 are steroid nitrite/nitrate compounds and are particularly relevant for the group of compounds falling under claim 10 and further claims having this structural feature.

The compounds of the formula given in claim 10 only differ through the meaning of the group R^2 (cf the case that R^2 is $OC(O)R^8$).

The problem underlying the present invention is considered to be the provision of further compounds which are useful in the treatment of oxidative stress and free radical injury (e.g. respiratory, inflammatory and autoimmune diseases).

In view of the similarity in structure with the claimed compounds, it is considered that the skilled person would have readily expected the componds in the claims to have the desired anti-inflammatory activity.

It may be noted in this context that claim 10 and further claims cover numerous

compounds not having the characteristics of the examples given in the description. Thus, there are greater generalisations in structure going from the examples to the claims than there are structural differences with the prior art compounds of D10.

The compounds of the present application are desribed as having a SOD mimic component, which is not disclosed for the compounds of D10. However this cannot in itself be considered a therapeutic action and still needs to find a therapeutical application in the form of a defined pathological application in order to make a technical contribution to the art. In the present the compounds of the application and those of D10 appear to have the same therapeutic action i.e. they are antinflammatory

The problem underlying the invention is thus considered to be the provision of further compounds having a surprising effect compared to the compounds of the closest prior.

During the PCT examination procedure, the Applicant gave arguments and results in order to demonstrate the superiority of the claimed compounds.

It is however considered that the above did not adequately form the basis for the acknowledgment of an inventive step.

Thus, in the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compounds of the present application having the maximum structural similarity with the compounds of the closest prior art, such that the effect is shown to have its origins in the distinguishing feature of the invention. Since these requirements have not as yet been fulfilled an inventive step cannot as yet be acknowledged.

VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 to D14 are not mentioned in the description, nor are these documents identified therein.

VIII

The term "alkyl" as used in the claims would not normally be understood as covering

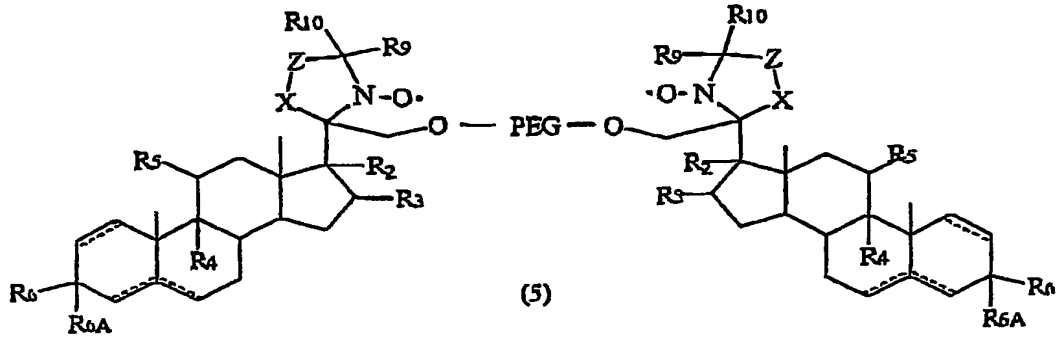
cyclic alkyl or substituted alkyl groups as given on page 22 of the description. Similar discrepancies can be found for the terms "aryl" and "heteroaryl".The function of the claims is to define the matter for which protection is sought. In view of this the meaning of the terms of a claim should as far as possible, be clear for the person skilled in the art from the wording of the claim alone. This is not the case for the said terms leading to further clarity objections.

R^6 is =O, —ONO, —ONO_2, —SNO, —NONOate;

R^{6A}, if present, is —H, or R^6 and R^{6A} together form a substituted N-oxide free radical;

R^7 is —H, —ONO, —ONO_2, —SNO, —NONOate, or a substituted N-oxide free radical wherein the nitrogen of the N-oxide group in the substituted N-oxide free radical is within a 5- or 6- member ring, which ring is optionally substituted by —$OCOCH_2$-PEG wherein said PEG may by optionally coupled to another steroid compound, and which ring is further optionally substituted by or one or more independently selected C_1-C_5 alkyl groups which may be further independently substituted by a group selected from an NO donor component, —SR^{11}, —halogen, and —$OC(O)R^{13}$ wherein R^{11} is C_1-C_5 alkyl and wherein R^{13} is C_1-C_5 alkyl or 5- or 6-member heteroaryl, or R^2 and R^7 together form a substituted N-oxide free radical; and wherein NO donor is a group comprising one of —ONO_2, —ONO, —SNO, and —NONOate, and wherein the nitrogen of the N-oxide group in the substituted N-oxide free radical is within a 5- or 6- member ring substituted by one or more independently selected C_1-C_5 alkyl groups which may be may be further independently substituted by an NO donor component; and with the proviso that said compound contains at least one N-oxide free radical and at least one NO donor.

This invention also relates to a dimer steroid compound in which PEG links two, preferably identical, steroid structures, preferably selected from Ia to Id, IIa to IId, IIa to IIId, and IVa to IVd



(5)

wherein the R^2, R^3, R^4, R^5, R^6, and R^{6A} are as defined above;

heteroaryl; and R^9 and R^{10} are independently, linear or branched C_1-C_5 alkyl groups, or substituted linear or branched C_1-C_5 alkyl groups, wherein said alkyl group may be is independently substituted by —ONO, —ONO_2, —SNO, —NONOate or —$OC(O)R^{14}$, wherein R^{14} is C_1-C_5 alkyl, or 5- or 6-member heteroaryl.

24. A multifunctional steroid compound comprising
i) a steroid component,
ii) at least one SOD mimic component, and
iii) at least one NO donor component,
for use as a medicament.

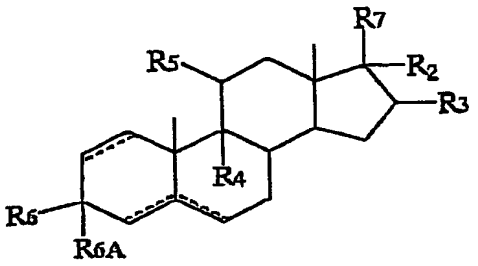
25. A multifunctional steroid compound according to claim 24, wherein said steroid component is selected from corticosteroids, estrogens, progesterones, androgens, analogs thereof, and derivatives thereof.

26. A method of treating or preventing a disorder selected from the group consisting of asthma, chronic bronchitis, bronchiectasis, bronchospasms, emphysema, Chronic Obstructive Pulmonary Diseases (COPDs), bronchial hyperreactivity, respiratory distress syndrome or Chronic Obstructive Airway Disease (COADs), allergic conditions, arthritis, autoimmune hematologic disorders, systemic lupus erythematosus, systemic dermatomyositis, thrombocytopenia, psoriasis, contact dermatitis, atopic dermatitis, exfoliative dermatitis, acne, hirsutism, erythema nodosum, inflamed cysts, discoid lupus, bullous diseases, collagen vascular diseases, malignancies, neoplastic disease, trauma, shock, acute and chronic inflammatory conditions, sarcoidosis, Sweet's disease, graft-versus-host disease, multiple sclerosis, Alzheimer diseases, Parkinson's diseases, amyotrophic lateral sclerosis, convulsive disorders, AIDS-dementia, disorders related to learning, disorders related to olfaction, disorders related to nociception, cerebral edema, migraine, ophthalmic disorders, chronic adrenal insufficiency, congenital adrenal

subcutaneous injection, implant, inhalation spray, nasal, vaginal, rectal, sublingual, and urethral.

30. A method according to claim 26, wherein said mammal is human.

31. A multifunctional steroid compound of formula (4) —



(4)

optical isomers thereof, salts thereof, and solvates thereof;

wherein ----- is a single or double bond, with the proviso that two double bonds are not adjacent;

R^2 is NO donor —H, OH, —CH_3, —$OC(O)R^8$ wherein R^8 is C_1-C_5 alkyl or 5- or 6-member heteroaryl, or or R^2 and R^7 together form a substituted N-oxide free radical;

R^3 is —H, —OH, or —CH_3, or R^2 and R^3 together form a heterocyclic ring;

R^4 is —H or halogen;

R^5 is —H, =O, NO donor, or a substituted N-oxide free radical;

R^6 is =O, NO donor, and

R^{6A}, if present, is —H, or R^6 and R^{6A} together form a substituted N-oxide free radical;

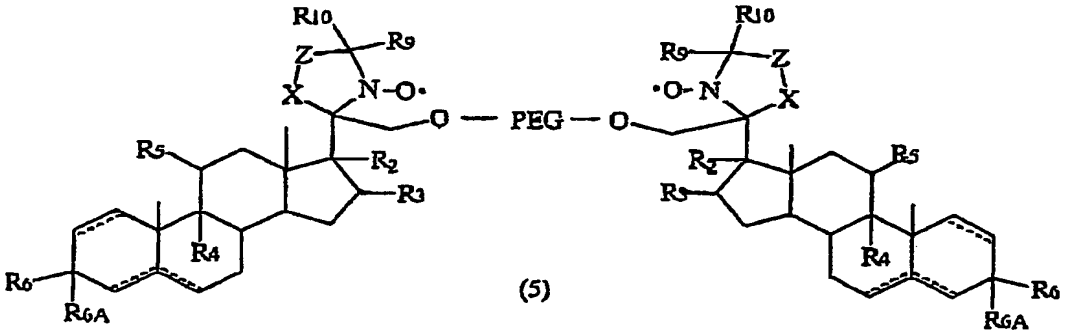
R^7 is —H, NO donor, or a substituted N-oxide free radical wherein the nitrogen of the N-oxide group in the substituted N-oxide free radical is within a 5- or 6-member ring, which ring is optionally substituted by —$OCOCH_2$-PEG wherein said PEG may by optionally coupled

to another steroid compound, and which ring is further optionally substituted by or one or more independently selected C_1-C_5 alkyl groups which may be further independently substituted by a group selected from an NO donor component, —SR^{11}, —halogen, and —$OC(O)R^{13}$ wherein R^{11} is C_1-C_5 alkyl and wherein R^{13} is C_1-C_5 alkyl or 5- or 6-member heteroaryl, or R^2 and R^7 together form a substituted N-oxide free radical; and

wherein the nitrogen of the N-oxide group in the substituted N-oxide free radical is within a 5- or 6- member ring substituted by one or more independently selected C_1-C_5 alkyl groups which may be further independently substituted by an NO donor component, and wherein said NO donor is a group comprising one of —ONO_2, —ONO, —SNO, and —NONOate; and with the proviso that said compound contains at least one N-oxide free radical and at least one NO donor.

32. A multifunctional steroid compound according claim 31, wherein said PEG links two identical structures selected from the group consisting of Ia to Id, IIa to IId, IIa to IIId, and IVa to IVd.

33. A compound according to claim 32, having formula (5)



(5)

wherein the R^2, R^3, R^4, R^5, R^6, and R^{6A} are as defined in claim 31;

R^9 and R^{10} are independently, linear or branched C_1-C_5 alkyl groups, or substituted linear or branched C_1-C_5 alkyl groups wherein the alkyl group is